Clinical Guide to Navigating the Landscape of Biosimilars for Inflammatory Bowel Disease

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Abstract: Annual out-of-pocket expenditures for patients with inflammatory bowel disease (IBD) are estimated to be as high as $41,000, with medications, such as biologics, being one of the main cost contributors. Although biologics have revolutionized IBD management, these medications are costly owing to their molecular makeup and manufacturing processes. Biosimilars, which are biologic medications that are highly similar to the US Food and Drug Administration (FDA)-approved reference product with no clinically meaningful differences in safety, purity, or potency, offer the same therapeutic benefits at a reduced cost. Other additional benefits offered with biosimilars include increased treatment access and fostered development of new therapeutic options. Despite the expansion of biosimilars in IBD, their adoption and utilization have been suboptimal in the United States. This article provides an overview of the biosimilar landscape in IBD, including FDA-approved biosimilars available, and a clinical guide to navigate switching to biosimilars in various clinical scenarios based on current evidence.

Keywords
Biosimilars, infliximab, adalimumab, pipeline, inflammatory bowel disease, biologics

Biologic treatment has revolutionized the management of inflammatory bowel disease (IBD), resulting in clinical and endoscopic remission, reduced hospitalizations and surgeries, and improved patient quality of life.[1,2] However, because of the intensive molecular development and complexity of biologics, they are expensive to produce. Direct out-of-pocket annual costs associated with IBD management incurred by patients has been estimated to be as high as $41,000, with medication costs driving approximately 51% of that expenditure.[3] The high cost of medication places a significant burden on patients and may lead to deferment of essential follow-up or prescription fulfillment, resulting in increased complications associated with uncontrolled IBD.[4] Further contributing to the financial burden for patients is the growing incidence of earlier utilization of biologic treatment in the course of IBD to achieve optimal outcomes and reduce disease progression and complications.[5,6] Access to these agents can be difficult for some depending on their insurance coverage.

Table. Biosimilars Currently Available in the United States for Inflammatory Bowel Disease Treatment

Biosimilar	Manufacturer	FDA approval	Indications
Infliximab biosimilars			
Avsola (infliximab-axxq)	Amgen	2019	CD (adult/pediatric), UC (adult/pediatric), RA, AS, PsA, Ps
Inflectra (infliximab-dyyb)	Pfizer	2016	CD (adult/pediatric), UC (adult/pediatric), RA, AS, PsA, Ps
Renflexis (infliximab-abda)	Organon	2017	CD (adult/pediatric), UC (adult/pediatric), RA, AS, PsA, Ps
Adalimumab biosimilars[a]			
Abrilada (adalimumab-afzb)[b]	Pfizer	2019	RA, JIA, PsA, AS, CD, UC, Ps, HS, UV
Amjevita (adalimumab-atto)[c,d]	Amgen	2016	RA, JIA, PsA, AS, CD, UC, Ps, HS, UV
Cyltezo (adalimumab-adbm)[b-d]	Boehringer Ingelheim	2017	RA, JIA, PsA, AS, CD, UC, Ps, HS, UV
Hadlima (adalimumab-bwwd)[d]	Organon/ Samsung Bioepis	2019	RA, JIA, PsA, AS, CD, UC, Ps, HS, UV
Hulio (adalimumab-fkjp)[c]	Mylan/Fujifilm Kyowa Kirin Biologics	2020	RA, JIA, PsA, AS, CD, UC, Ps, HS, UV
Hyrimoz (adalimumab-adaz)[b-d]	Sandoz	2018	RA, JIA, PsA, AS, CD, UC, Ps, HS, UV
Idacio (adalimumab-aacf)	Fresenius Kabi	2022	RA, JIA, PsA, AS, CD, UC, Ps, HS, UV
Simlandi (adalimumab-ryvk)[b]	Alvotech/Teva	2024	RA, JIA, PsA, AS, CD, UC, Ps, HS, UV
Yuflyma (adalimumab-aaty)	Celltrion	2023	RA, JIA, PsA, AS, CD, UC, Ps, HS, UV
Yusimry (adalimumab-aqvh)	Coherus BioSciences	2021	RA, JIA, PsA, AS, CD, UC, Ps, HS, UV

[a]For UC, HS, and UV, adalimumab biosimilars are indicated for adults only, whereas the reference product is indicated for adults and pediatric pts.

[b]Contains interchangeable designation and could be substituted for reference product at pharmacy level.

[c]Has unbranded formulation available.

[d]Both high and low formulations are available; the low formulation may not be citrate-free.

AS, ankylosing spondylitis; CD, Crohn's disease; FDA, US Food and Drug Administration; HS, hidradenitis suppurativa; JIA, juvenile idiopathic arthritis; Ps, plaque psoriasis; PsA, psoriatic arthritis; pts, patients; RA, rheumatoid arthritis; UC, ulcerative colitis; UV, uveitis.

As a solution to address the increased costs and limited treatment access, pharmaceutical companies have introduced biosimilars, which are biologic medications that are highly similar to their US Food and Drug Administration (FDA)-approved reference product with no clinically meaningful differences in safety, purity, or potency.[7] Biosimilars have been well adopted in many European countries, resulting in several benefits, including expanded and timelier access to biologic treatment and increased access to innovative medicines.[8] As of 2022, the cumulative savings generated with biosimilars in Europe exceeded €30 billion (US $32.6 billion).[9] Conversely, biosimilar adoption and utilization in the United States has been suboptimal despite biologic treatment comprising 46% of total medicine spending and projected estimates that biosimilars could generate up to $181 billion in savings.[10] Potential barriers to use include concerns about biosimilar efficacy and safety, uncertainties about product availability and utilization as hindered by litigation, and financial logistics related to rebates and reimbursements.[11] Given the growing financial burdens associated with IBD treatment and the potential for biosimilars to reduce costs, increased biosimilar utilization should be part of cost-effective IBD management. This article reviews biosimilar-related concepts and provides a clinical guide to navigate the biosimilar landscape in IBD.

Biosimilar Concepts

Biosimilars are developed from the same type of living source and administered by the same route, frequency, and dosage. These medications also produce efficacy and safety effects comparable to the reference product, essentially providing the same treatment benefits but at a lower

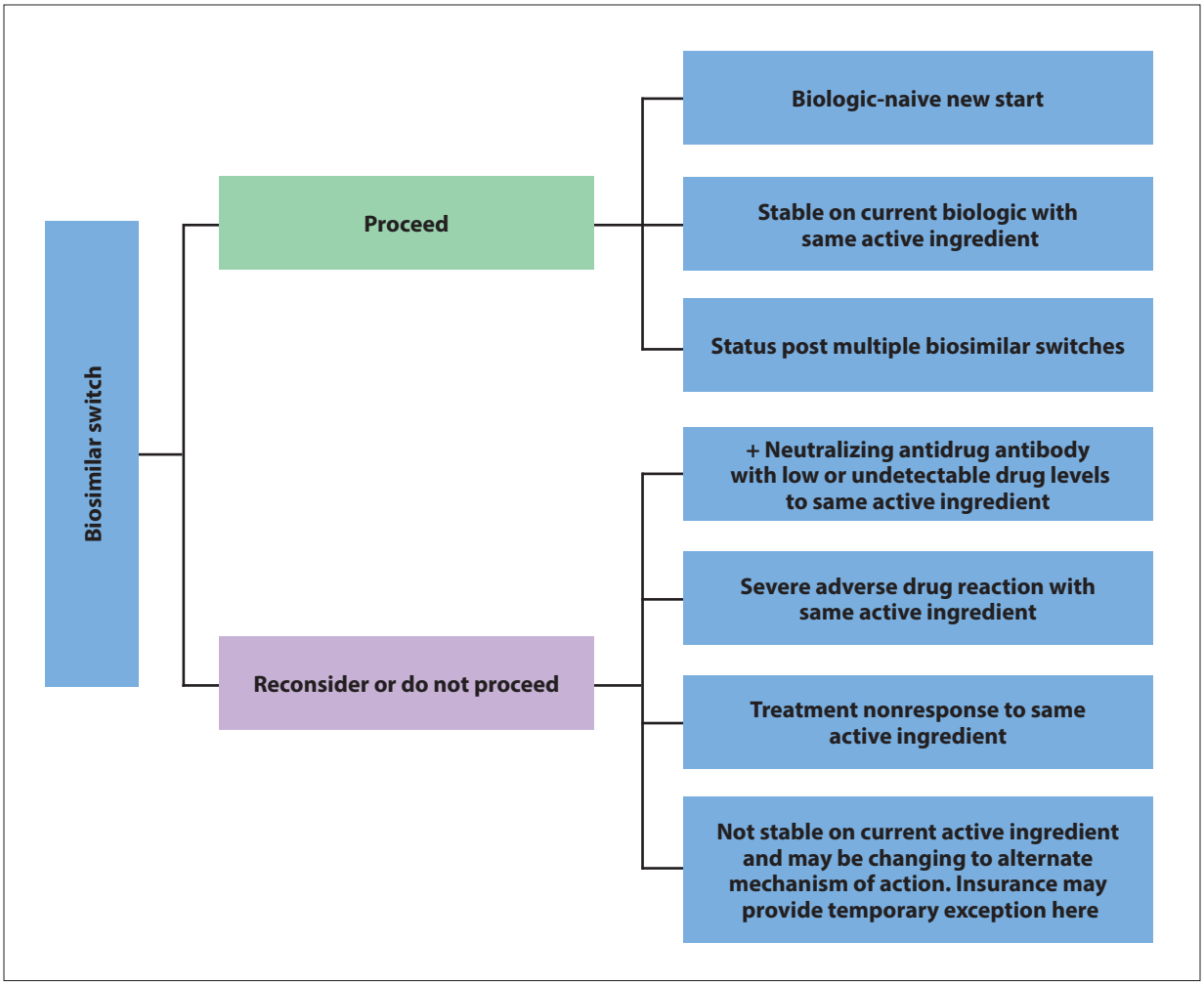

Figure. Flow chart to handle biosimilar switching in various clinical scenarios.

cost.[7] Biosimilars undergo a robust FDA review process; as long as biosimilarity to the already FDA-approved reference product is demonstrated through structural and functional studies, extensive large-scale studies evaluating biosimilar clinical effectiveness in each individual disease state are not warranted.[12,13] Rather, through the concept of totality of evidence (consisting of structure/function studies, animal studies, and clinical studies designed to assess pharmacokinetic and pharmacodynamic properties), the FDA can approve the biosimilar to be used in indications already approved with the reference product, a process known as extrapolation. Collectively, this FDA pathway allows biosimilars to undergo a less costly, but still robust, evaluation process.

If the biosimilar manufacturer provides additional evidence that their biosimilar will produce the same clinical results as the reference product in any given patient and that alternating between the biosimilar and reference product multiple times does not generate any additional risks when compared with continuing the reference product, the FDA may grant an interchangeability designation for that biosimilar.[7] Interchangeable biosimilars can be substituted and dispensed for the reference product at the pharmacy level without the approval of the prescribing provider, depending on state pharmacy laws. The interchangeability designation does not indicate superiority over other biosimilars and is a status specific to the United States; in Europe, all biosimilars are automatically considered interchangeable. Unbranded products, which are the generic form of the reference product or biosimilar that is marketed without its brand name, are also entering the market with the intent to further compete with biosimilars at comparable pricing while still retaining market shares.

A list of all currently available infliximab and adalimumab biosimilars (some of which are interchangeable, as well as some products that are unbranded formulations

of infliximab and adalimumab) indicated for IBD is provided in the Table. The FDA approved 2 biosimilars for ustekinumab: ustekinumab-auub (Wezlana, Amgen), which is interchangeable, in 2023; and ustekinumab-aekn (Selarsdi, Teva Pharmaceuticals) in 2024. However, litigation settlement terms dictate that these biosimilars will not be available for patient use until 2025.[14] Other pharmaceutical companies are in the process of developing ustekinumab biosimilars but have also made a similar settlement agreement with the reference product manufacturer to delay their product launch to 2025 even if FDA approval is obtained sooner.[15] Biosimilars for vedolizumab are not anticipated to enter the US marketplace until 2032.[16]

Although most infliximab and adalimumab biosimilars received FDA approval for use in IBD through the process of extrapolation, many published studies and real-world evidence from Europe demonstrate that biosimilars result in similar patient outcomes as expected with the reference product, such as sustaining remission without increased adverse effects or immunogenicity risks.[17-19] Additionally, interchangeability studies have shown pharmacokinetic equivalence and comparable safety with multiple switches between the adalimumab reference product and biosimilar.[20,21] Thus, biosimilars in IBD are effective and safe and can produce the same clinical outcomes at a much reduced cost, further decreasing financial burdens while improving patient outcomes and access.

Clinical Guide for Navigation

Because medication formularies influence prescribing practices and medication use within the United States, biosimilar adoption and utilization to date has been primarily driven by institutions or payers. However, implementing a successful workflow can ensure effective biosimilar uptake and smooth transition for patients already established on the reference product.[13,22,23] As more biosimilars emerge, with some being designated as interchangeable, prescribing and transcribing practices will need to be refined to be consistent and accurate. For example, electronic health record (EHR) systems need to be configured to provide ordering options for both brand and unbranded products. If a biologic is switched for an interchangeable biosimilar at the pharmacy, communication efforts should be streamlined and the EHR should be updated to reflect which biosimilar the patient is on. Simultaneously, progress notes and medication lists should contain accurate medication names. Additionally, everyone on the health care team should discuss reference biologics using their base name (eg, infliximab, adalimumab) instead of brand name (eg, Remicade, Humira) to further highlight the availability of biosimilars containing the base active ingredient and improve patients' awareness and confidence with biosimilar treatment. Assigning one staff member in the practice to be the biosimilar champion can help with streamlining processes while maintaining real-time and updated educational initiatives for both providers and patients. Prior authorization requirements for patients switching to a biosimilar have been variable among payers. Thus, it is critical to ensure that adequate resources and support are in place for this process. Patients who are informed of a switch request should receive education that pursuing an appeal of this request in most clinical scenarios is inappropriate and predominantly unsuccessful. An appeal could also lead to treatment interruption or delay, which is more detrimental than switching to the covered biosimilar. Patients initiating injectable biosimilars will also need additional education relating to administration of their new device, which can be provided by the pharmacy team or manufacturer-related resources, including online training videos or nursing support. Lastly, implementing a monitoring program would be helpful for patients concerned about biosimilars to help mitigate negative sentiments against these agents and potential for treatment discontinuation. Biosimilar navigation strategies for various clinical scenarios are further explored in the following section and outlined in the Figure.

Clinical Scenario #1

Initiating a Biosimilar in a Biologic-Naive Patient Given the earlier utilization of biologic treatment, it is becoming more common to encounter biologic-naive patients, which requires a more nuanced discussion to include not just brand-named products but also biosimilars. In addition to using the biologic base name when discussing treatment options and educating patients on biosimilars, physicians should discuss the potential for a future switch of the current biosimilar to a biologic or another biosimilar based on payer and formulary coverage. The preferred medication on the formulary should be prescribed, and patients should be connected to that medication's resources and programs.

Clinical Scenario #2

Switching From a Reference Product to a Biosimilar for the First Time Biosimilar transition in the IBD population may be challenging because of prior disease experiences. Switching medications can instill fear or concerns in patients about potential relapse and disease flare or worsening. Ongoing proactive education about biosimilars with emphasis on the same base active ingredient, dosing, and clinical outcomes prior to the switch is preferred to prepare patients before they are notified about the need to switch. Again, referring to the patient's

medication by the base name instead of brand name is recommended to reduce misperceptions relating to biosimilars being ineffective or inferior. For patients needing to switch, ensuring that the prior authorization is completed in a timely manner to avoid treatment interruptions, providing education on self-injectable devices, and connecting patients to the right resources (eg, copay assistance, nurse ambassador support) will be essential for a smooth transition. Routine monitoring of disease and treatment outcomes should be continued.

Of note, current evidence indicates no changes in clinical outcomes with switching to a biosimilar.[24] Thus, there is no clinical basis to deter switching in a patient who still has not achieved clinical remission on a current biologic. However, from an operational standpoint (eg, for a patient who is transitioning from inpatient to outpatient or who recently started treatment and is in the induction phase), payers may be willing to cover the current product on a short-term basis until the patient is stabilized or identified as needing an alternate treatment after receiving several doses of a new start. If the coverage request is not approved or the determination is taking longer than anticipated and may cause a treatment delay, it is recommended to switch the patient to a biosimilar as soon as possible and continue to provide proactive education and monitoring.

Clinical Scenario #3

Switching From Biosimilar to Biosimilar As more biosimilar and unbranded products enter the market and payers and institutions continue to evaluate cost-related considerations, formulary changes are expected to become more frequent, making a biosimilar-to-biosimilar switch more commonplace. Presently, the FDA only approves a biosimilar in comparison to its reference product and not to another biosimilar. Regardless, multiple switches are becoming more common with payer- and institution-enforced mandates. Current evidence shows comparable efficacy and safety in patients undergoing multiple switches vs patients who underwent a single or no switch.[25-27] Again, prior authorization should be completed in a timely manner to avoid treatment interruptions, and appropriate education (eg, injection training, medication resources) should be provided as needed. Additionally, the EHR, progress notes, prescriptions, and therapy plans should be accordingly updated to reflect the current product that the patient is on, and routine clinical monitoring should be continued.

Clinical Scenario #4

Pregnancy Current recommendations for optimal pregnancy and birth outcomes in patients with IBD emphasize that remission in a healthy mother is the cornerstone for healthy babies and birth outcomes.[28] Because it is common practice to exercise caution when taking medications during pregnancy and risks in pregnancy with use of some biologics and their biosimilars may be unknown, the IBD population may have reservations about switching to a new medication during pregnancy. Biosimilars have not been associated with congenital abnormalities, preterm birth, or other adverse pregnancy outcomes; conversely, treatment interruption can be detrimental. Thus, pregnant patients on a biologic who are required by their insurance carrier to switch to a biosimilar or unbranded product should ideally do so to reduce treatment delays.[29] Patients or clinicians who opt to defer switching until completion of pregnancy may be able to request temporary coverage of the current treatment but should be prepared to switch if that request is denied. Again, completion of the prior authorization in a timely manner, provision of education about administration and resources, and routine clinical monitoring are important elements in the transition process.

Clinical Scenario #5

Inappropriate Biosimilar Use or Switch Given the overlap in mechanism of action between the biosimilar and reference product, certain patients, such as those who develop antidrug antibodies, have a severe adverse drug reaction (eg, drug-induced lupus), or experience treatment nonresponse with the base active ingredient, should not be placed on a biosimilar product with the same base active ingredient. Additionally, some payers have implemented a criterion that the patient must either try and fail a biosimilar before the reference product will be covered or vice versa.[30] This criterion is not clinically sound because when the mechanism of action of a medication fails to produce a response in a patient, use of the same mechanism through a different product will not produce a different outcome.

Clinical Scenario #6

Patients on a Biosimilar With Adverse Effects or Treatment Dissatisfaction As with biologics, the treatment effect of biosimilars should be objectively assessed with standard laboratory tests and procedures such as fecal calprotectin, colonoscopies, and imaging. If remission is confirmed, the biosimilar treatment should ideally be continued, and necessary steps (eg, premedications) should be taken to address any existing adverse effects. A switch back to the prior product may be possible if the insurance carrier permits, and continued monitoring should be provided. If patients lose treatment response after the switch, it is important to educate that loss of response to the overall mechanism can occur with biologic medications and is not necessarily representative of biosimilar efficacy or safety.

A systematic review that evaluated efficacy and safety outcomes of a switch from a reference product to a biosimilar in double-blind vs open-label studies found higher discontinuation rates occurring in the open-label studies. The authors attributed the finding to a nocebo effect, defined as adverse effects occurring with a treatment that cannot be attributed to the treatment effect. This well-established phenomenon is associated with increased risk of biosimilar discontinuation and nonacceptance. As mentioned previously, the best approach to mitigate biosimilar negativity is to provide proactive biosimilar education, refer to the base name instead of the brand name, and reassure patients that clinical care and monitoring remain the same. Additionally, employing a shared decision-making process when a switch scenario occurs can help address patients' concerns and empower patients in their care.[32,33] Prior studies have demonstrated that patients rely on health care providers to develop biosimilar confidence and comfort.[34] Thus, it is important for all members of the health care team to be up-to-date on biosimilar news and evidence and to project a positive, confident perception of these medications.

Biosimilar Considerations

Biosimilars are projected to have tremendous impact in IBD care; however, there are areas where their benefits could be improved. For commercially insured patients who were previously enrolled in a copay assistance program for the reference product, switching to a biosimilar may not yield significant cost savings. According to a cohort study using a national commercial claims database, patients' annual out-of-pocket spending did not decrease after the start of biosimilar competition.[35] Although it is hoped that biosimilars may lead to lower insurance premiums down the line, which would then directly benefit patients, it would be more impactful if patients experienced real-time direct cost savings with biosimilar utilization.

With the introduction of biosimilars, many health care systems and institutions have observed increased administrative burdens, especially with prior authorizations and medication coordination, including prescribing and biosimilar education. If an institution has an infusion center or associated specialty pharmacy, there may be opportunities for cost savings or revenue. In general, the staff members involved in biosimilar efforts are not reimbursed or aware of any direct benefits from maximized workflow efficiency with biosimilars. Similarly, it would be impactful if prior authorization requirements were removed or if payers reimbursed the institution's staff for supporting and overseeing biosimilar adoption and utilization.

Conclusion

Biosimilars can offer many significant benefits, including reduced financial burden on patients and the health care system, increased treatment access, and fostered development of newer therapeutic options. Use of these treatments in IBD has the potential to be extremely impactful given the utilization of biologic treatment earlier in the disease course and growing incidence of patients with IBD needing these effective treatments. Currently in the United States, multiple biosimilars are available for infliximab and adalimumab, with more biosimilars in the pipeline for ustekinumab and vedolizumab. Full integration of biosimilars into IBD practice has been hindered by several barriers. However, with the implementation of a biosimilar champion to manage the workflow, the biosimilar landscape can be easily navigated and optimized in IBD care.

Disclosures

Dr Bhat has served on advisory boards for Boehringer Ingelheim and Pfizer and as a consultant to AbbVie. Dr Kane has been a consultant for Boehringer Ingelheim, Celltrion, Fresenius Kabi, Janssen, and Takeda.

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